Changes in Chondriosomes Occurring in Pathological Conditions.

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With 11 Text-figures.

The structural characters of chondriosomes were first investigated in detail by Benda[1] in a number of different cell types (renal cells, spermatids, marrow cells, leucocytes, striated muscle).

Subsequently Meves,[2] by means of embryological observations, studied the metamorphoses of chondriosomes[3] in relation to differentiation of cell function, and showed that thereby different types of fibrils resulted, such as the cytoplasmic fibrils of epidermal cells, the fibrils of striped and unstriped muscle, neurofibrils, neuroglia fibres and connective-tissue fibres.

Although the structural characters of chondriosomes have been studied in detail, nevertheless the delimitation of mitochondria is in some cases still uncertain, and the full significance of chondriosomes in respect of cell function has yet to be determined. It has, however, been found possible in some cases, especially in respect of secreting cells, to form a

[1] Benda, "Weitere Mitteilungen über die Mitochondria," 'Verh. d. Phys. Ges. zu Berlin,' 1899.

[2] Meves, "Die Chondriosomen als Träger erblicher Anlagen, Cytologische Studien am Hühnerembryo," 'Arch. f. Mikr. Anat.,' 1908, B. 72, S.

[3] Mitochondria (*μίτος*, a thread; *χόνδρος*, a grain) are granular; chondriokonts (*κοντός*, a pole) are rod-like. Chondriosome (*σῶμα*, a body) is a general term applied to both varieties. Illustrations are given in the figures.

conception of the significance of these granular or rod-like structures found in cytoplasm. Thus it has been shown by Regaud[1] that chondriosomes form the matrix of the secretory granules in the cells of the convoluted tubules of the kidney, and G. Arnold,[2] in an investigation upon the secretory activity of pancreatic cells, has traced the formation of zymogen granules by the maturation of chondriosomes.

Various theories have been advanced in explanation of the significance of chondriosomes in relation to cell functions. Benda regarded chondriosomes as representing a contractile constituent of the cell. Meves[3] has advanced the hypothesis that they are carriers of hereditary functions. More recently Regaud,[4] following Altmann and J. Arnold, has attributed to chondriosomes the function of fixing and concentrating various substances in the cell (fonction électique, Renaut)—an hypothesis which, as he observes, is not opposed to that of Meves, the two hypotheses rather representing different points of view. The conception of function advanced by Regaud is in complete harmony with the behaviour of chondriosomes in relation to secretion as exhibited by the cells of secretory glands.

Observation does not appear to have been up to the present directed to the study of chondriosomes in morbid cell states. Such investigation, however, appears likely to throw further light upon the significance of these cell structures.

In the present paper the condition of the chondriosomes is

[1] Regaud, C. L.—"Participation du chondriosome à la formation des grains de ségrégation dans les cellules des tubes contournéss du rein (chez les ophidiens et les amphibiens)." 'Compt. Rend. de la Soc. de Biologie,' 1909, t. 66. p. 1034.

[2] Arnold, G., "The rôle of the chondriosomes in the cells of the guinea-pig's pancreas," 'Arch. f. Zellforschung,' 1912, B. 8. S. 252. Cp. L. Launoy, "Contribution à l'étude histo-physiologique de la sécrétion pancréatique," 'Arch. Internat. Phys. Liège,' 1905, vol. iii.

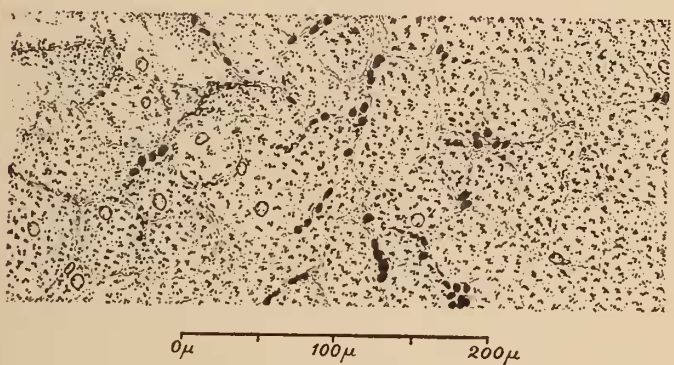
[3] Meves.—Loc. cit.

[4] Regaud, C. L.—"Sur la signification physiologique du chondriome des cellules sexuelles mures, notamment des spermatozöides." 'Compt. Rend. de la Soc. de Biologie,' 1909, t. 66, p. 443.

investigated in respect of three pathological cell states, namely: (1) in that obtaining in the cells of the liver when pigmentary degeneration has occurred; (2) in that obtaining in the convoluted tubules of the kidney during severe hæmoglobinæmia; and (3) in the epidermis when a marked degree of epithelial proliferation has been set up. In all these cases examination of chondriosomes is readily effected, special methods of chondriosomal fixation not being required, and

FIG. 1.

[The scale of figs. 1, 2, 5 and 6 is given below fig. 1; that of figs. 3, 4, 7, 8, 9 and 10, below figs. 3 and 4.]



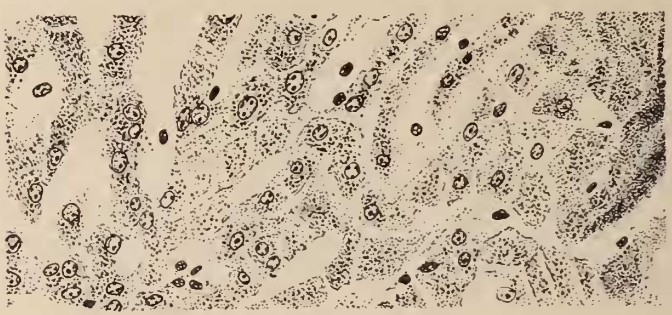
Section of liver of healthy rabbit. The liver-cells are closely apposed, the usual arrangement in cell columns being obscured. The blood-capillaries are indicated by red blood-cells darkly stained. The cytoplasm of the liver-cells exhibits numerous chondriosomes, appearing as deeply stained granules which obscure or conceal the nuclei. Fixed in Flemming's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 200.

thus the uncertainty and difficulty of chondriosomal staining is avoided. In the case of the liver and kidney it will be necessary, before studying the chondriosomes in the pathological state under consideration, to describe the normal appearance presented by the latter structures. It may be observed that in the liver and kidney, as in other secreting glands, the chondriosomes retain the embryonic type of

granule or rod throughout life, not undergoing any metamorphosis.

In the cells of the lobules of the liver of the adult rabbit fixed in Benda's or Flemming's solution, and stained by Heidenhain's iron-alum hæmatoxylin method (figs. 1 and 3), only mitochondria are normally met with. These are spherical or oval in shape, and are usually 0·6 μ to 1·0 μ in their greatest length, but the latter measurement may be exceeded, and, on the other hand, granules 0·2 μ or less in diameter may be met with (fig. 3). The mitochondria are sharply outlined, and are

Fig. 2.



Section of liver of rabbit, exhibiting pigmentary degeneration. The liver-cells, which exhibit the normal arrangement in branching columns, contain dark pigment-granules, similar in size and arrangement to the chondriosomes shown in fig. 1, but less numerous. Fixed in Zenker's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 200.

scattered irregularly throughout the cytoplasm of the liver-cells, not being definitely arranged in chains or groups. They appear to vary in number. It is not, however, possible to determine accurately the number of chondriosomes present in a single cell owing to the difficulty of defining the exact limits of the hepatic cells. Nevertheless, seventy may be regarded as an approximate estimate of the number present in a single hepatic cell. The varieties observed in the chondriosomal content of healthy liver-cells in different rabbits (illustrated

by figs. 3 and 4), are apparently related to the functional or nutritive condition of the cell.[1]

The appearance of the pigment-granules (unstained) in the liver-cells in pigmentary degeneration (figs. 2 and 4) is, apart from their coloration, indistinguishable from that of the mitochondria (shown in fig. 3). The granules are spherical or oval in shape, and are scattered irregularly throughout the cytoplasm. Those shown in fig. 4 are 0·3 μ to 0·6 μ in length, but smaller (0·2 μ) and larger (0·8 μ) forms are also met with. The number of chondriosomes present in a single cell is

FIGS. 3 (to left) AND 4 (to right).

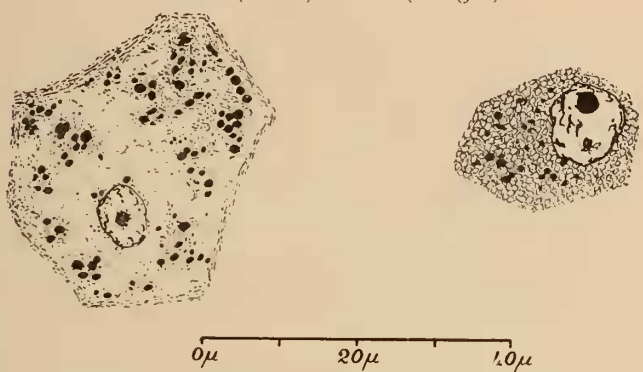


FIG. 3.—Liver-cell from fig. 1, more highly magnified. The chondriosomes, which are abundant, assume the form of well-defined, deeply stained granules, more or less ovoid in shape, ranging from 0·5 μ to 2·0 μ in diameter and arranged in groups. Fixed in Flemming's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 1000.

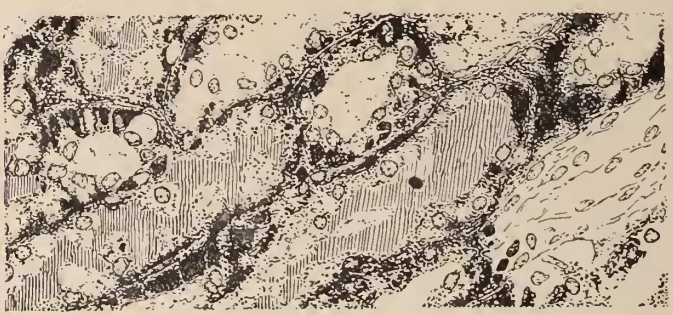
FIG. 4.—Liver-cell from fig. 2, more highly magnified. The cytoplasm is denser than in the cell shown in fig. 3 and exhibits a meshwork arrangement; it contains black (unstained) pigment-granules, which in appearance and size closely resemble the chondriosomes shown in the preceding figure, but are fewer in number. Fixed in Zenker's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 1000.

[1] The rabbit from which figs. 2 and 4 were made was somewhat thin but seemed otherwise normal; its liver-cells were small in size, the cytoplasm being dense and presenting a finely vacuolated structure. The rabbit from which figs. 1 and 3 were made was exceedingly well nourished; its liver-cells were large, the cytoplasm being abundant.

approximately seventy, the variations met with not appearing to be considerable. The identity of the pigmented granules with mitochondria at once becomes obvious when a comparison of the two is made. The appearance of liver-cells, stained with hæmatoxylin, containing the former is indistinguishable from that of normal liver-cells similarly stained after treatment with mitochondrial fixatives (such as Benda's modification of Flemming's solution). In both cases the mitochondria appear of a deep black colour.

In sections of the kidney of healthy adult rabbits fixed in

Fig. 5.



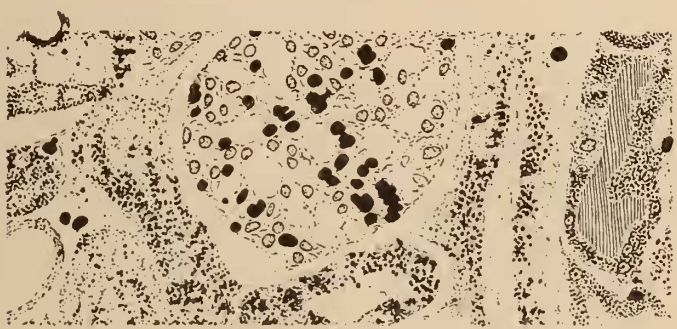
Section of kidney of healthy rabbit at junction of cortex and medulla. The cells of the convoluted tubules shown in the section present a granular aspect, due to the presence in the cytoplasm of deeply stained chondriosomes, the nuclei tending to become obscured in consequence. A few red blood-cells, deeply stained, are seen lying between the tubules. In the lumen of three of the tubules hyaline material is seen. Fixed in Flemming's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 200.

Benda's solution, and stained by Heidenhain's iron-alum hæmatoxylin method, the chondriosomes which are met with in the cells of the convoluted tubules[1] assume the form of rods and granules. In some of the cells only mitochondria are seen; in others—and this is more usually the case—chondriokonts are also met with, situated near the basement mem-

[1] I have not met with chondriosomes in the cells of the glomeruli.

brane, to which they are attached by one extremity, mitochondria being distributed throughout the cell elsewhere. In fig. 5 the appearance of the healthy kidney with the chondriosomes stained is shown under a low magnification, which, while showing indications of granules and collections of rod-like forms, does not permit of the arrangement of the chondriosomes being traced in detail. In fig. 7 a convoluted tubule cell taken from fig. 5 is shown under a higher magnification. Only mitochondria, it will be observed, are seen, but elsewhere in the same section cells conforming to the type

Fig. 6.



Section of cortex of kidney of rabbit during marked hæmoglobinæmia. A glomerulus is seen, within the capillaries of which are red blood-cells deeply stained, but no granules are present. Several convoluted tubules are shown, the cells of which contain darkly stained granules, many of which are larger than those exhibited in fig. 5. The largest granules are disposed next to the lumen of the tubules. Hyalin material fills the lumen of the tubule lying to the right of the section. Fixed in Zenker's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 200.

shown diagrammatically in fig. 9 are found. The mitochondria which are distributed throughout the cytoplasm resemble those already described, being sharply outlined, spherical or oval bodies, ranging from 0·5 μ to 0·8 μ in diameter; occasionally they reach 1·0 μ in diameter; in other cases they do not measure more than 0·2 μ across. The chondriokonts assume the form of short rods, sometimes very

fine, sometimes coarse, occasionally thicker at the end, and not unfrequently presenting a flattened-out appearance. They measure 0·5 μ to 0·8 μ in thickness, and reach about 4·5 μ in length. The number of chondriosomes in individual convoluted tubule cells could not be accurately determined, but appeared to be approximately about fifty.

In sections of the kidney of a rabbit suffering from severe hæmoglobinuria following injection of a large amount of hæmoglobin (obtained from rabbit's red blood-cells) (fig. 6), or of a dog suffering from hæmaturia due to piroplasmosis, the renal cells exhibited chondriosomes, readily stained by Heidenhain's iron-alum hæmatoxylin method, after the

FIGS. 7 (to left) AND 8 (to right).

FIG. 7.—Renal cell taken from fig. 5, more highly magnified. The cytoplasm contains deeply stained chondriosomes, assuming the form of more or less oval granules 0·5 μ to 2·0 μ in diameter. Near the basement membrane these granules are small; towards the free surface large granules are seen. Fixed in Flemming's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 1000.

FIG. 8.—Renal cell, taken from fig. 6, more highly magnified. Near the basement membrane, chondriosomes, deeply stained, of small size and more or less elongated, are seen in the cytoplasm; towards the free surface of the cell large chondriosomes, reaching as much as 4 μ in length, are observed. (The large, darkly stained mass lying wholly within the nucleus is a nucleolus; below and to the right of this is a large chondriosome lying upon the edge of the nucleus.) Fixed in Zenker's solution. Stained by Heidenhain's iron-alum hæmatoxylin method. × 1000.

use of fixatives such as Zenker's solution and formaline which do not permit of the staining of chondriosomes in the normal kidney of the rabbit. As was first described and

figured by Yorke,[1] the cells of the convoluted tubules in such conditions are filled with granules which may be of unusually large size and are recognisable under a low magnification (fig. 8). Rod-like forms may also be present, but owing to their small size are not well seen. The granules which are situated towards the lumen of the tubules are well defined, more or less rounded in aspect, and reach as much as 2 μ to 2·5 μ in diameter, granules of this size being fairly numerous, while in exceptional cases a diameter of 6 μ may be reached; the smaller granules measure 0·5 μ to 0·8 μ across, the smallest granules being, however, 0·2 μ or less in diameter. These granules are irregularly scattered and exhibit no definite

FIGS. 9 (to left) AND 10 (to right).

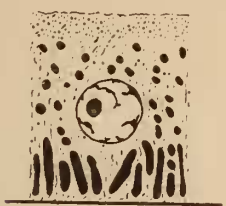


FIG. 9.—Type of normal cell of convoluted tubule prior to excretory activity. The chondriosomes consist of chondriokonts, lying near the basement membrane, and mitochondria, arising from the chondriokonts, and forming an outer granular layer reaching to the striated border of the cell. × 1000.

FIG. 10.—Type of cell of convoluted tubule in severe hæmoglobinæmia. The condition of the cell is indicative of extreme secretory activity. The chondriokonts are much finer than in the preceding figure, while the mitochondria and secretory granules are numerous and of unusually large size. × 1000.

grouping. The rod-like forms shown in fig. 8 are slender and are situated more deeply than the granules, one end being attached to the basement membrane; their thickness usually ranges from 0·3 μ to 0·4 μ, their length being about 3 μ. The number of rods and granules observed in the cells of the convuluted tubules appeared to be approximately the same as in normal cells. In some cells no chondriokonts could be seen, only mitochondria being observed. The smallest

[1] Yorke, W., "The Passage of Hæmoglobin through the Kidneys," 'Annals of Tropical Medicine and Parasitology,' 1911, vol. 5, p. 401.

granules are in the unstained condition colourless; the larger granules are brownish, the depth of colour being proportional to their size. The coloured granules stain less deeply with hæmatoxylin than the smallest granules.

The granules and rods just described are obviously chondriosomes, some of which are larger than in the normal condition. The identity of the forms seen in hæmoglobinæmia with chondriosomes is here more strikingly exhibited than is the case in the instance furnished by the pigmented liver of the rabbit, for we are dealing with two types, namely, rod-like forms and granules, and in both the normal and pathological condition the passage of rod-like forms into granules can be observed. For convenience of comparison of healthy and abnormal renal chondriosomes, a semi-diagrammatic representation of the two types is afforded by figs. 9 and 10.

Regaud[1] has shown that in Ophidia and Amphibia the secretory granules of the kidney, which are discharged into the lumen of the convoluted tubule, arise in relation with the mitochondria, and these in turn are formed from chondriokonts. This author figures the chondriokonts and secretory granules in the different stages of secretory activity of the renal cells, pointing out that the former are least numerous when the latter are most abundant and vice versâ. The cell shown in fig. 8 and represented diagrammatically in fig. 10 resembles an exaggerated degree of the condition figured by Regaud as that immediately preceding excretion, but it is not improbable that the functions of the cell represented in fig. 8 have in reality become disordered to such an extent as to imperil the integrity of the cell. The brownish colour of the larger granules during hæmoglobinæmia indicates the part taken by these structures in the elimination of hæmoglobin.

The significance of the pigmentary change exhibited by the cells of the liver is difficult to estimate, the relation of the chrondriosomes to the secretory activity of these cells being

[1] Regaud.—Loc. cit.

unknown. It may, however, be observed that the functions of the hepatic cells in such cases do not seem to be seriously affected, for the condition is not incompatible with continued existence.

The chondriosomes of the epidermis have long been known as epidermal fibrils (fibrilles epidermiques, Protoplasmafasern), though their relation to chondriokonts has only recently been established by the researches of Firket.[1] So far back as 1899, Herxheimer[2] pointed out that these fibrils are most readily demonstrable in epithelioma, in warts, and in the apparently healthy skin in the neighbourhood of these lesions. Epidermal fibrils can also be exhibited with varying degrees of facility in callosities, at the edge of lupus areas and in chronic inflammatory conditions. In all these lesions, however, staining is more or less uncertain and is unequal in different parts of the same section. When overgrowth of epidermis has been produced in human skin or in the skin of the rabbit by means of the epidermal cell proliferant Scharlach R.[3] epidermal fibrils are much more easily exhibited, and the condition of the skin, both in respect of the extent to which cell hypertrophy takes place, and of the degree to which the chondriosomes become stained, can be modified by varying, on the one hand, the amount or concentration of Scharlach R introduced into the skin, and, on the other hand, by suitably choosing the period after injection at which the skin is sectioned, so that excellent preparations exhibiting the condition of the epidermal fibrils may in this way be obtained. The effect of the dye, like that of hæmoglobin in

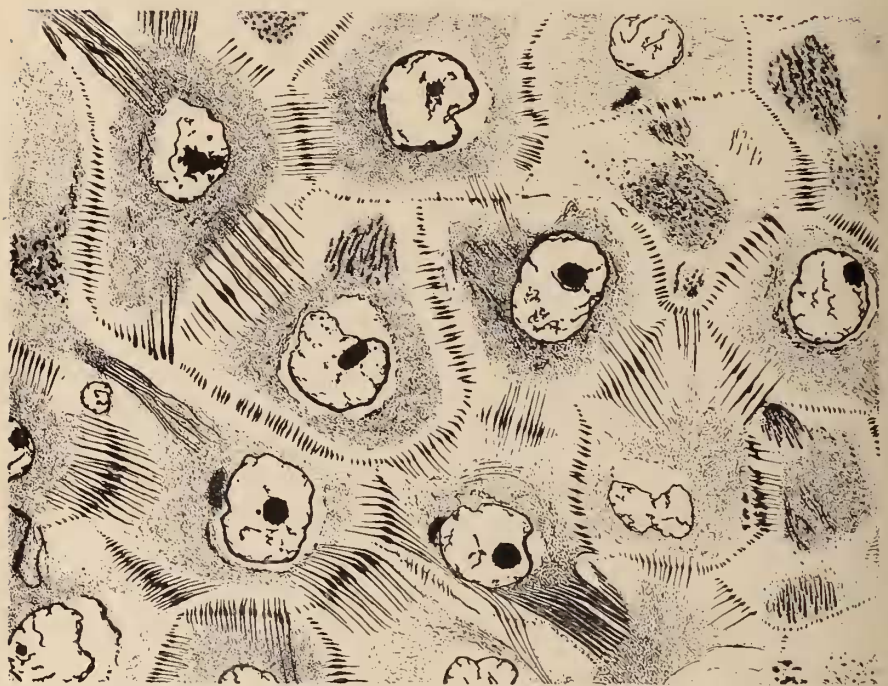
[1] J. Firket —"Recherches sur la génèse des fibrilles épidermiques chez le poulet," 'Anat. Anz.,' 1911, Bd. xxxviii.

[2] K. Herxheimer.—"Über eigentümliche Fasern in der Epidermis und Epithel verschiedener Schleimhäute," 'Arch. f. Dermatol. u. Syph.,' 1889, Bd. xxi.

[3] B. Fischer.—"Die experimentelle Erzeugung atypischer Epithelwucherung und die Entstehung bösartige Geschwülste," 'Münch. med. Wochenschr.,' 1906, 53 Jahrg., S. 2041; J. O. Wakelin Barratt, "Implantation of actively proliferating Epithelium," 'Proc. Roy. Soc.,' 1907, ser. B., vol. lxxix, p. 546.

the case of the kidney, may in fact be compared to that of a mordant, enabling structures to be exhibited which would otherwise remain unstained or stain very imperfectly. The action of Scharlach R is, however, exerted only upon the prickle layer; in the stratum granulosum, stratum lucidum and stratum corneum the fibrils are not demonstrable, though

FIG. 11.



Section of rapidly proliferating Malpighian layer of human epidermis. Epidermal fibrils are seen passing from cell to cell with varying degrees of obliquity. At the junction of the fibrils of adjacent cells nodular thickenings are seen forming the "prickles" of the Malpighian cells. The fibrils, which are arranged in bundles, pursue a curved course through the protoplasm of the prickle-cells, passing round the nucleus and then passing out of the cell again. When viewed at right angles to their length the fibrils present a sheaf-like arrangement; if seen lying in the axis of vision the surfaces of the cells present a hairy aspect. × 2200.

the nodular junctions of the fibrils passing between adjacent cells are still recognisable.

The appearance of the prickle layer of the epidermis when undergoing active proliferation is shown in fig. 11. The epidermal fibrils are seen to be arranged in bundles or sheath-like collections which pass from cell to cell. Within the cells the fibrils can be traced through the cytoplasm; they do not enter the nucleus, though frequently lying near the nuclear membrane as the figure illustrates. Although many of the fibrils entering the cell can be seen to pass out of the cell again, nevertheless the exact distribution of the fibrils in the prickle-layer is complex and difficult to follow out in its entirety. At the junction of the fibrils of adjacent cells a variable degree of thickening occurs, spindle-like nodules being thereby produced. When a number of such nodules are seen on the flat in optical section, as is shown in several cells in the upper half of fig. 11, a remarkable prickly or hirsute appearance is presented. The fibrils are of nearly uniform thickness throughout their course in the cell protoplasm.

The extent to which chondriosomes are altered in conditions involving active cell proliferation cannot be estimated with great precision owing to the impossibility of satisfactorily exhibiting the chondriosomes of the epidermis in perfectly healthy skin, for the methods of fixation and staining at present available usually reveal only the nodular thickenings at the points of junction of the fibrils of apposed cells, the fibrils themselves either remaining unstained—and this is the usual event—or staining imperfectly. As has been already mentioned, our knowledge of epidermal fibrils has been for the most part obtained by the study of the epidermis in pathological conditions. Judging by the appearance of the nodular junctions, it would seem that the chondriosomes in conditions of epithelial proliferation are markedly hypertrophied. Whether in addition any increase in the number of the fibrils or any change in their distribution in the cell protoplasm also occurs cannot at present be determined.

Summary.

(1) The mitochondria of hepatic cells in pigmented degeneration of the liver assume a brownish-black colour and form the pigment-granules characteristic of this condition.

(2) In severe hæmoglobinæmia the chondriosomes of the cells of the convoluted tubules are more readily demonstrable than in the normal condition, their staining capacity being increased. In this condition the mitochondrial elements reach an abnormally large size and are observed to take part in the elimination of hæmoglobin.

(3) In pathological conditions in which rapid cell proliferation is occurring, the chondriosomes of the prickle layer of the epidermis appear of large size and stain with unusual facility, details of their structure being readily observable. In this respect they contrast with normal epidermal chondriosomes, which stain imperfectly.